CEREBRAL REGULATION OF MOTOR COORDINATION IN MONKEYS FOLLOWING MULTIPLE TRANSECTION OF SENSORIMOTOR CORTEX

R. W. SPERRY
Department of Anatomy, The University of Chicago, Chicago, Illinois[1]

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THE FOLLOWING experiments are concerned with the problem of the role in cerebral function of horizontal intracortical transmission. The plan was to see how much functional disorganization would result from extensive surgical subdivision of a cortical field by numerous vertical knife cuts extending just through the depth of the cortex. Such incisions would leave the cortical subdivisions interconnected by axons looping through the white matter but would at the same time block all direct interchange of excitations through the gray matter itself. The result should furnish an indication of the functional importance of *intra*cortical, as distinguished from *inter*cortical, integration.

The arm area of the cortex was selected because convenient criteria of its organized function are available in the coordinated movements of the arm, particularly in the refined manipulative "voluntary" movements of the hand and digits (10). In coordinated arm movements, the action at each joint of the limb must be regulated with reference to the action at all the other joints, and also the movement of the arm as a whole must be directed with respect to the posture and action at joints in the rest of the body. Cerebral regulation of arm movement would seem accordingly to require an integrated interaction or interplay of some kind among the various electrostimulable foci in the cortex for movement of these separate parts. It was proposed to find out what functional effect would follow the separation of these cortical foci from one another in the foregoing manner by a series of multiple intersecting incisions.

For the following reasons, one might predict the above to cause only negligible disturbance of function. (i) Slicing of the cortical gray with a thin sharp knife need produce only a minor amount of direct damage to neuron cell bodies. (ii) Study of the cortical cytoarchitecture has indicated that local linkages occur primarily in vertical chains (24), and therefore cuts in the vertical plane should disrupt only a minimum of neuron interrelations. (iii) The majority of association fibers to and from other cortical fields and

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subcortical structures course downward through the white matter and hence would be left intact by incisions restricted to the depth of the cortex.

On the other hand, there are a number of facts and theoretical considerations which pre-indicate that any such partitioning of a cortical field would more probably lead to profound disruption of its functional organization. The incisions would necessarily interrupt any horizontal intracortical spread of excitations via long horizontal fibers or via the plexus of innumerable short intracortical connections. They would also interrupt or at least cause extreme distortion of any spread through the cortex of "field forces" such as mass electrical potentials. That horizontal spread or irradiation of excitation patterns in the cortex plays a very important role in the functional organization of the cerebrum has been widely assumed. Pavlov (28) especially considered cortical irradiation to be a fundamental principle of cerebral activity and explained many aspects of the learning and conditioning process in terms of it. Although his specific concept of cortical irradiation has been attacked sporadically, the general idea has continued to remain a significant influence in the theory of cerebral function.

The assumption that excitations radiate horizontally along the fiber network of the gray matter has to some extent been verified experimentally with electrical recording methods. Adrian (1) described the outward spread of potential waves from a stimulated point across the cortex at speeds of the order of 10–40 cm. per second. The propagation was attributed to conduction of activity from neuron to neuron in the deeper cortical layers. It was emphasized that the character of these radiating potentials was unnatural owing to depression of the cortex by anesthesia and the artificial means of initiation, *i.e.*, by electrodes, but these potentials are considered to be indicative of at least a kind of activity that probably occurs in the normal brain. Rosenblueth, Bond and Cannon (29, 30) also have reported a type of spreading intracortical potential which they found did not cross a cut in the gray matter and the transmission of which was ascribed to the feltwork of fibers in the cortex. These intracortical potentials are capable of inhibiting and facilitating impulses entering the area involved. McCulloch (25) mentions the capacity of the cortex to exhibit intracortical spread of self-sustained discharges and the necessity of taking precautions to avoid these when mapping the intercortical connections by the strychnine method. He points out that it is not certain whether the intracortical transmission is by neuronal paths in the cortical fiber feltwork or by chemical changes induced in neurons by repeated firing of cells in their neighborhood. A slowly spreading depression of activity which is blocked by shallow incisions through the pia and outer three layers of the cortex has been described by Leao (21) and by Leao and Morison (22). Bucy and Fulton (4, 5) have reported that contralateral limb responses not unlike those obtained from stimulating area 4 can be elicited from area 6 when the cortex is intact but not after a superficial incision through approximately half the depth of the gray has been made at the boundary separating areas 4 and 6. From this and the fact that

the same responses are not affected by undercutting area 6, it was concluded that the reactions involve transmission of excitations from area 6 to area 4 through a system of superficial intracortical fibers.

Although experimental findings like the foregoing have suggested possible mechanisms and organizing influences of horizontal intragriseal irradiation, the status of the actual role of such intracortical transmission in normal integrated behavior has continued to remain highly speculative. Integrative effects of utmost importance have been ascribed to radiating waves of intracortical excitations in Lashley's (17, 19, 20) "reduplication" or "wave interference" hypothesis of cortical organization which was proposed to account for sensory equivalence and correlated phenomena of memory. In this hypothesis impulses entering the cortex are assumed to set up spreading waves of excitation transmitted over the largely homogeneous feltwork of fibers in the gray. These radiating waves in their interplay are assumed to establish reduplicated interference patterns throughout the given cortical field. It is these secondary interference patterns rather than the initial stimulus patterns which are considered to be effective in the translation into motor function and which form the basis of sensory pattern recognition and memory. A series of close intersecting knife cuts extending through the gray mantle ought clearly to cause a severe derangement of any cortical organization based on interference patterns of this sort.

In addition to the functional disturbances to be anticipated from the interruption of definitive intracortical axon pathways and neuron circuits, impairment of integration might also be expected to result merely from disturbing the continuity of the gray matter as a physicochemical medium with properties en masse for maintenance and conduction of electrical potentials and currents. Intercellular electrical fields and currents flowing through and between neurons have recently been suggested by Gerard (12, 13) and Libet (23) to be perhaps the most significant factor in the interaction of nerve cells in large groups and masses, overshadowing even the part played by the more commonly recognized potentials conducted along fiber pathways. Their papers present much direct experimental evidence with many additional references gathered in support of this thesis. They list the following important aspects of central nervous function as being more readily explainable on the basis of these massive field currents and potentials than in terms of impulses transmitted over discrete anatomical pathways: (a) the spontaneous electrical beat of neurons and their synchronization; (b) the establishment of new functional neural connections between brain centers in conditioning; (c) central nervous inhibition; (d) the mass functioning of the cortex in learning; (e) the summation of excitatory and inhibitory impulses reaching separate neuron processes; (f) total behavior patterns; and (g) the phenomenon of sensory equivalence. Obstruction or distortion of the mass electrical fields and currents subserving these basic integrative phenomena would be expected accordingly to result in marked symptoms of disintegration and malfunction.

An all-important role in cerebral organization has long been ascribed to intracortical "field forces" in the postulates of the Gestalt school of psychologists. These hypothetical "field forces" in their most concrete form (16) have been described as electromotive forces generated by chemical excitation processes. They supposedly set up patterns of electrical currents which pervade the cortical tissue in and about any incoming excitations. It is these mass electrical patterns which are contended by this school to be the basis of perception and the effective factor in organizing motor responses. The dimensions of such force fields in the cortex may presumably be quite large, covering, for example, most or all of the visual striate area. Since these organizing field forces are dependent upon relatively homogeneous physicochemical properties in the cortical matrix, they would of necessity be drastically disarranged by partitioning a cortical area with numerous intersecting vertical lesions.

Minor references from other sources in which significant integrative effects have been attributed to horizontal "polarization of cortical fields," "irradiation of excitation patterns across cortical centers," "peaks of electrical gradients in the cortex," etc., might be added in further support of the prediction that vertical partitioning of the sensorimotor arm area would cause extreme distortion of its organized function.

Such a forecast is favored further by the probability of causing functional loss merely by the direct traumatic effects of such lesions. Adverse chemical effects from the damaged tissue, ischemia, and diffuse lowering of excitatory state owing to the cutting off of excitations and trophic effects from adjacent regions are among some of the accessory factors that might be expected to contribute to a depression of function. On the other hand, survival of apparently organized function in isolated cortical remnants has been recorded in a few instances (2, 18). This in itself would tend to counterindicate the importance to cerebral organization of intracortical irradiation, but this type of evidence has not been considered decisive on this point.

On the whole, the information available for predicting the results of surgical subdivision of a cortical field is meager and largely theoretical. The present effort to test the question experimentally was undertaken because of the direct bearing of the matter on the foregoing theories dealing with problems of the fundamental nature of cerebral integration.

METHODS AND MATERIALS

The animals used were mostly *Macaca mulatta* in two groups. Those of the first group (cases 1–5) were about 4 years old and weighed approximately 10 lbs. each. Those of the second group (cases 6–9) were about 2 years old and weighed approximately 5 lbs. each. Two adult spider monkeys (*Ateles geoffroyi*) weighing approximately 10 lbs. (cases 10 and 11) were also used. The sensorimotor arm area was selected in addition to the reason already mentioned because of its convenient location on the lateral surface of the hemisphere, and because its subjacent fibers tend to approach the cortex vertically in such a way that knife cuts accidentally slipping into the white matter would produce less damage to projection fibers than in areas where the subjacent fibers run tangentially. Anesthesia was induced with ether and maintained with intraperitoneal injection of sodium amytal. A bone flap was turned down, large enough to permit full exposure of the sensorimotor arm area

of the cortex. The precentral gyrus was then stimulated electrically and movements of the contralateral leg, arm and face were noted to determine the medial and lateral limits of the arm area. The anterior and posterior boundaries of the area to be subdivided were determined by characteristic cortical landmarks (7).

Intersecting transverse and longitudinal incisions approximately 2.4 mm. apart were then made subpially through the gray matter in various gridiron patterns as illustrated in the figures. The cutting instruments were constructed from fine stainless steel wire or #12 sewing needles bent into the desired shape, soldered to a steel handle, and ground and honed under a stereoscopic microscope into an extremely thin double-edged blade. The blade was constructed on a right angle so that it could be inserted into the cortex through a small puncture of the pia, and having been moved horizontally underneath the pial membrane to make the desired cut, withdrawn through the same hole leaving the pial blood vessels intact (see Fig. 1A). Incisions into the depths of the fissures were made with a blade of different shape as shown in Fig. 1B. The back of the knife was passed downward along the

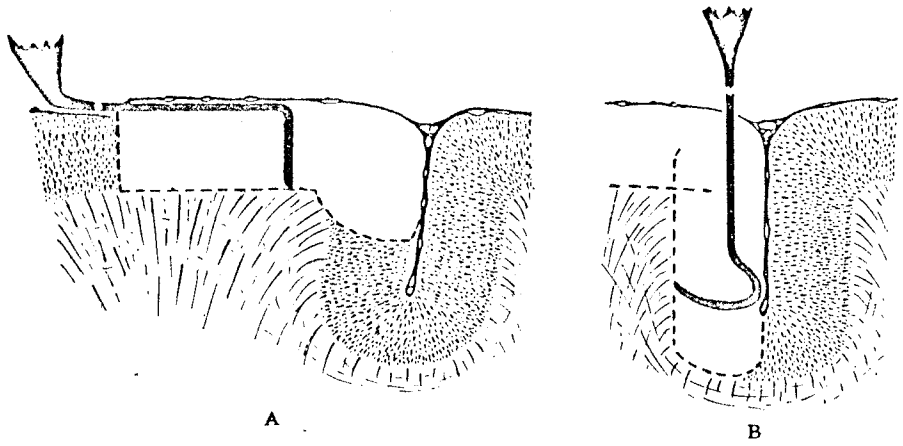


FIG. 1. Diagrams drawn in plane of incisions to illustrate the two types of knives used and how cuts were made at a gauged depth with minimal damage to pia and blood supply, (A) in cortex exposed at surface and (B) in fissures.

involuted pia to the proper depth and then withdrawn in the same path. All lesions were made with the aid of a dissecting microscope with a magnification of 10.5 times.

The upper edge of the cutting instrument could be seen clearly through the transparent pia as it severed the outer cortical layers directly against the under surface of the pial membrane. With the knife in close contact with the pia in this manner the minimum depth of the incisions was automatically determined by the dimensions of the cutting blade. Occasional slipping of the knife some fractions of a millimeter deeper into the cerebrum was unavoidable, however, and although any missed outer layers were severed by retracing, the deeper cuts into the white matter below could not be repaired. The knife was purposely run deeper in regions where the cortex is thicker, as at the lips of fissures. The 90° angle at which the blade was held and moved with respect to the pia proved fairly easy to maintain.

The cutting procedure avoided the surface vessels, but bleeding occurred from interruption of the smaller vessels and capillary beds in the gray matter. Blood immediately filled the subpial incisions, pushing the cut surfaces apart and pouring out of the small pial puncture where the blade was inserted. This collection of blood in the incisions always made the lesion pattern clearly visible. Under the microscope a map of the completed lesion pattern and associated fissures was traced on cellophane as recommended by Fulton (11), and retraced in pencil on another paper while the image of the operative field was still fresh in mind. The final figures were then made from these two maps, or directly from the brain itself after fixation. The depth of the incisions was later determined by histological examination.

A definite decrease, but not complete cessation, of blood flow in the surface vessels in the affected area probably a result of the mechanical stimulation (9)—was commonly noticed. Special care was taken to keep the exposed pia well moistened with thin cotton pledgets saturated with body fluids absorbed from the operative field. When the cellophane tracing was completed, the dura was sutured into place with fine silk thread, the bone flap was tapped back into position, and the galea and skin closed separately over it. When it was necessary to give extra anesthesia while the incision was being closed, ether was used rather than more amytal because of the temporary effect of ether and its tendency to dilate the cerebral blood vessels. Also as an aid to maintaining good cerebral circulation, the hind quarters were kept slightly elevated after the cortical transectioning had been started. A bandage was applied and removed about eight days later.

The sensorimotor arm areas of both hemispheres were operated upon in nearly all cases, the second side being done two weeks or more after the first with the exception of case 10. Arm, hand, and finger coordinations were observed during and shortly after recovery from anesthesia, at daily intervals during the following two weeks, and at increasing intervals thereafter. In estimating the effects of the operations on motor coordination, a large variety of natural cage and special test performances were observed, including voluntary and reflex, learned and automatic reactions of varying speed and complexity. Particular attention was paid to the delicate "voluntary" manipulative movements of the hands and fingers. No special attempt was made to test sensory capacities beyond the extent to which they were indicated by the motor performances. The affected limbs were compared with the contralateral limbs and with the limbs of normal animals and also with the limbs of control cases in which the corresponding cortical areas had been completely destroyed. In some cases, following recovery, the subdivided motor area was exposed, stimulated electrically and then excised to determine further its functional status.

At the time of sacrifice the brains were perfused with 10 per cent formalin and subsequently sectioned and stained for nerve cell bodies with cresyl violet and for myelin by the Weil method.

CASE HISTORIES

Cases 1 and 2, right hemisphere. The portion of the precentral arm cortex exposed on the surface of the hemisphere was partitioned in the first two animals by a pattern of incisions like that illustrated in Figure 2 (case 1) with a knife blade 2.9 mm. in length. This was found to cause no detectable disruption of motor coordination as judg ed by general cage activities. Even very fine delicate movements of thumb and fingers in manipulating food and grooming were displayed by the affected hand in both cases during the first three days after operation. As early as four hours after operation case 1, for example, ate eagerly and performed the following acts with the left hand. The hand was stretched full length through the cage wires and was used to pick up pieces of orange and apple. Pieces of food were raised to the mouth with the left hand alone. The thumb was opposed to the fingers in holding the food. While the monkey was chewing and biting off pieces of food, the food was held and manipulated by the affected hand with much differential pronation and supination of the wrist, all well coordinated with movements of the digits and elbow. A piece of orange peel was twisted strongly between thumb and fingers so as to bend it inside out. The bandage was scratched effectively at the forehead with the tips of the fingers. The wrist was flexed and its dorsum was pushed against the food pouch to empty it in the typical manner. Small bits of apple skin were neatly removed from between the lips by thumb and fingers. Crumbs of food which fell into the fur of the leg and foot were picked out delicately with the thumb and fingers of the left hand.

The only symptoms of motor deficit which could be detected in these two animals were a slight muscular weakness on the affected side and some preference for use of the normal hand, both of which were evident only during the first few days after operation. The muscular weakness showed up in movements of pulling at the head bandage and in quick reactions of the hand and arm as in attempts to catch flies in flight, but even in such movements the difference between the two hands was not striking. The hand preference was only statistical in nature and was readily counteracted as early as a few hours after operation by offering food from the side of the affected arm.

Case 3, left hemisphere. To obtain some indication of how close together such partitioning incisions might be made without disrupting function a lesion pattern was made as shown in Figure 3 with the same knife used in cases 1 and 2. The cuts were made in the

left cortex of an animal which had not quite fully recovered from a severe paralysis of the left hand inflicted by a deep (6.5 mm.) circumsection of area 4a in the right hemisphere two months previously. The effect of these close incisions was definitely more noticeable than in the preceding cases, but the animal's pre-established preference for use of the right hand was not abolished. Immediately on recovery from anesthesia the right hand was used and continued thereafter to be used consistently in reaching for food and in bringing it to the mouth. The right hand continued to predominate in the manipulation of food at the mouth, in grooming, and in scratching at the bandage. Fine delicate coordinations of fingers, thumb, and wrist survived as in the previous cases. Lack of high speed and vigor in the movements, however, was apparent during the first several days after operation. Despite the consistent preference for the right hand, the fingers of the left hand appeared to

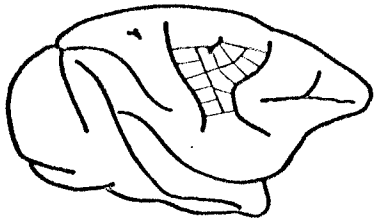


FIG. 2

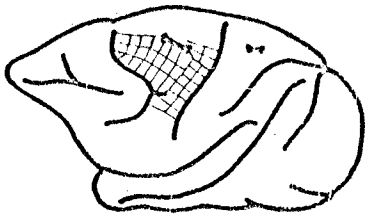


FIG. 3

be stronger when employed, for example, with the other hand in bending open an orange. The strength and speed of the movements of the right hand seemed to have been fully restored by the 9th day after operation.

To make the incisions closer together becomes technically difficult because the circumsected gray matter tends to break loose. Also interpretation of the results is complicated because the amount of tissue damage becomes a large factor. Furthermore, it is sufficient for the theoretical purpose for which the experiments were designed to subdivide the arm area into approximately four sections mediolaterally, separating from each other the foci for movement of shoulder, elbow, wrist, and digits. Therefore, instead of making the incisions closer together in subsequent operations, the incisions were extended to cover larger cortical areas.

Case 1, left hemisphere. In the next operation the partitioning incisions, made with the same 2.9 mm. knife, were extended posteriorly to include the exposed portion of the postcentral as well as the precentral arm area. The lesion pattern shown in Figure 4 was made on the left side one month after subdivision of the precentral arm cortex on the right side. Even this subdivision of the entire exposed surface of the sensorimotor arm cortex plus area 19 failed to cause elimination or distortion of the motor coordinations of the contralateral arm, hand, or fingers. The motor symptoms after recovery from anesthesia were only slightly, if at all, more severe than those following subdivision of the precentral region alone; namely, a slight weakness in manipulative movements and a statistical preference for the ipsilateral hand during the first few days after operation. Well-organized motor coordination survived in deliberate voluntary movements as well as in automatic reactions.

Case 4, control. A control case was next prepared in which the exposed surface of the precentral arm area and the arm portion of the postcentral gyrus were destroyed completely by the same method used in making the incisions except that the knife cuts were purposely run so close together as to damage the intervening tissue beyond repair. The result was a severe paralysis of the contralateral arm and hand. The first day after operation the arm could be used weakly in running, with some movement at the shoulder and elbow and usually enough at the wrist to place the hand palm down, but the hand was incapable of picking up or holding small objects. It did not even aid the contralateral arm in feeding. When the animal was frightened the fingers at times seemed to hook weakly on the cage wires, but no grip was shown when a stick was placed against the palm of the hand. The arm was never extended full length horizontally. With the elbow bent, however, it was occasionally raised under excitement to shoulder level. Most of the time during the first

week after operation the arm of this control case simply hung from the shoulder without movement.

Two weeks later when there had been only slight improvement in the use of the affected hand, mainly in movements of progression and climbing, a similar operation was performed on the other (right) hemisphere, causing a similar paralysis but a little more severe in the left arm. When thus made dependent upon the previously affected right arm, the animal started to employ this arm to pick up pieces of food and to hold them while eating. The finger movements of the right hand were weak and clumsy during the first few days after the second operation but improvement with use was fairly rapid thereafter until in six days food objects could be picked up and manipulated at the mouth with little apparent difficulty. Sticks and cage wires were held by this time with a weak but definite grip and the arm was used with moderate proficiency in climbing.

Recovery in the newly affected left arm meanwhile had shown little progress. It hung

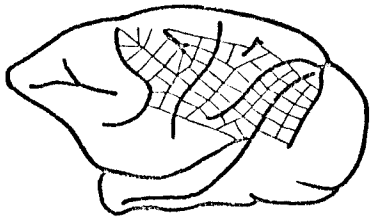


FIG. 4

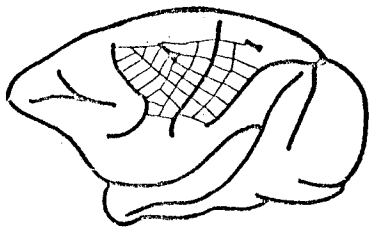


FIG. 5

at the animal's side most of the time and was practically useless even in climbing under intense excitement. Three weeks after the second operation the animal still had obvious difficulty in climbing about the cage and finger movements of the left hand were markedly clumsy. A month later when the animal was chased around in a large cage it tired easily, slipped and fell several times, and displayed a lack of agility indicating that recovery was still far from complete. Thus the severe paralysis caused by complete destruction of a cortical area in the control contrasted sharply with the negligible effect of transecting the same cortical area by vertical incisions.

Cases 2 and 5, left hemisphere. In two animals similarly operated upon—the lesion pattern of the first of which is shown in Figure 5—the incisions were extended into the depths of the central and arcuate fissures. This was done by sliding the knife blade down along the involuted pia to an average depth of approximately 8 mm. (see Fig. 1B). In case 2 the exposed precentral arm cortex on the right side had been subdivided about four weeks previously. The right cortex of case 5 had a lesion in the exposed precentral arm area which had produced partial paralysis about two and one-half months previously but from which the animal had recovered. The operations on the left cortex resulted in both cases in an obvious weakness but not a severe paralysis of the right arm. In spite of the greater area included in the transected field, the animals were still able immediately on recovery from anesthesia to use the affected arm to pick up small pieces of food, to bring the food to the mouth, and to hold it while eating, to reach up over the eyes to finger the bandage, and to make a fairly quick sweep of the hand at an annoying fly. The affected hand regularly assisted the contralateral hand in holding food at the mouth. However, the grip of the right hand was too weak to hold any but small pieces of food, like grapes, and the left hand throughout was definitely superior and preferred. This semiparalysis cleared rapidly in both animals until at the end of ten days little difference could be detected between the manipulative movements of the two sides.

In contrast, unilateral ablation of only area 4a of the arm cortex including the depth of the fissures but without damage to the postcentral gyrus has been shown to produce in adult macaques a profound, long-lasting, flaccid paralysis with recovery after a month of only clumsy finger movements (10).

Histology. Microscopic examination of the brains of the above animals revealed that the incisions in the regions posterior to the central fissure had extended completely through the gray matter and a short distance into the medulla both on the surface and in the walls

of the fissures. Anterior to the central fissure where the cortex is considerably thicker, the incisions for the most part extended well through layer V of the giant pyramidal cells and approximately through the upper one-third of layer VI. On the convexity of the precentral gyrus the cuts went somewhat deeper into the VIth cortical layer and completely through at some points. Where the lesions were continued into the fissures the incisions extended just below the bottom of the pial fold, leaving only a crescentic tip of the involuted gray matter intact. Where the cortical walls in the depths of the fissures become thinner, the cuts consistently extended into the white matter. Layer I subjacent to the pia was found to have been effectively divided throughout the partitioned area. Because of the transition zone of overlap between gray matter and medulla in the lower half of layer VI, particularly wide in the precentral areas, it is impossible to cut completely through the cortex without injury to fibers of the medulla. To make incisions deeper than the above, therefore, would of necessity entail increasing damage to the white matter. In the control case 4 only the exposed cortex was gone; the walls and depths of the fissures in the lesion area remained in good condition as was intended.

In summary, disturbance of function in this group of mature macaques was negligible where the incisions were confined to the exposed surface of the cortex without going deep in the walls of the fissures. Mass destruction of the same exposed cortical areas, by contrast, caused a severe paralysis which cleared slowly and was still evident over a month after operation. Inasmuch as the vertical incisions did not extend all the way through the VIth cortical layer in the precentral regions, a better control for comparison would involve destruction of only the upper five cortical layers, leaving VI intact. Exactly this type of lesion has been produced by laminar thermocoagulation by Murphy and Dusser de Barenne (26). They found that unilateral thermocoagulation merely of the superficially exposed portion of area 4a, leaving layer VI intact, produced in a macaque a typical long-lasting paresis that required two months for recovery.

When the incisions were extended into the depths of the fissures, a temporary partial depression of function resulted which disappeared in the course of about ten days. The symptoms were entirely those of muscular weakness. There were no convulsive, athetoid, or spasmodic reactions or other signs of discoordination to indicate disturbance of some important organizing mechanism. Complete destruction of the corresponding area including the depths of the fissures, on the other hand, produces a profound paralysis which is still marked after two months (see case 7 below) and from which recovery is probably never complete.

The experiments were continued with a series of younger rhesus monkeys whose age, calculated from their weight (31), was approximately two years. In these animals the incisions in the motor and premotor areas were all deeper than in the above group, made with knife blades which varied in depth in different individuals. In the sensory regions posterior to the central fissure the incisions were made at a constant depth in all cases with a knife blade of 2.7 mm. adjusted on the basis of the results in the first group to cut well through the gray matter. Attention was centered primarily on the late effects in this group because temporary depression of function was to be expected from cuts running into the white matter. Such lesions are, of course, permanent in both cortex and medulla due to the lack of nerve regeneration

in the mammalian central nervous system. Therefore recovery of motor function, even though it required some time, would indicate that the cerebral regulation of limb movement is not dependent upon any extensive transcortical interplay between separated motor foci of excitations transmitted through the gray matter.

Cases 6 and 7, right hemisphere. In case 6 the incisions anterior to the central fissure were made with a blade of 3.5 mm. in an intersecting pattern like that shown in Figure 6 and were confined throughout to the exposed surface of the cortex. This had almost no effect upon the automatic arm and hand movements of progression. Several hours after operation the affected hand was used to help the other in manipulating food and by the

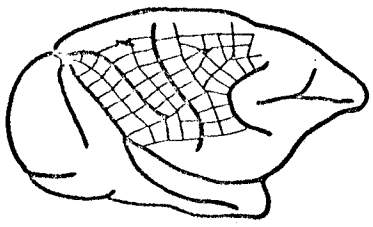


FIG. 6

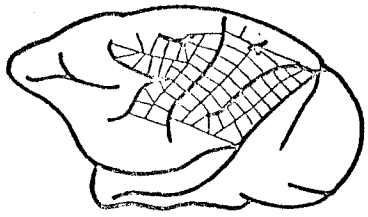


FIG. 7

second day after operation it was difficult to detect any difference between the right and left hands even in the finest movements.

When a pattern of cuts similar to that of case 6 was made in the right cortex of case 7 with a knife blade 5.0 mm. long, there was still but little effect on the rapid automatic movements of running and climbing. Manipulative movements, however, were effectively abolished by these deep cuts for three days, after which they returned gradually until by the 14th day the affected hand was again being used regularly to assist the other during feeding and occasionally to reach for objects. After the 20th day motor impairment was no longer evident when the affected hand was used, but preference for the other hand still lingered.

Subsequent microscopic examination of the incisions showed that they had gone well down through the gray matter in both the pre-and postcentral gyri in case 6. In case 7 the precentral incisions went more than twice as deep as the layer of Betz cells, *i.e.*, well into the white matter, and they extended more than half-way down the anterior wall of the central fissure.

In case 6 biopsy specimens of the subdivided precentral and postcentral gyri were excised for histological examination two weeks after the first operation and at the same time the remainder of the transected region was removed by suction. The result of this control operation was to abolish temporarily all manipulative movements and to decrease markedly the proficiency of the hand in climbing and running. On the fifth day the hand began to be used weakly to aid the other in feeding but it was not until the 11th day that any attempt was made with it to ward off a stick thrust threateningly toward the face. On the 22nd day the hand was used once in 12 trials to reach for and to pick up small pieces of food. By the 25th day the use of the left hand was almost normal again except for a persisting preference for the other hand. In this case the paralysis produced by excising a cortical area that had previously been partitioned provided additional evidence that the subdivided areas continued to function despite the extensive intersecting incisions.

At the same time it was clear that the paralysis produced by mass lesions in the exposed cortical arm area in these two-year-old animals was not so severe as in the older monkeys of the first series. The result of mass destruction was not itself profoundly disabling and long-lasting and consequently the difference between the experimental and control cases could not be as striking as it might otherwise have been. Accordingly, in the remaining operations the incisions were extended into the depths of the fissures in order to involve

sufficient cortex so that its mass destruction in control cases would cause more severe and lasting motor impairment.

Cases 6 and 7, left hemisphere. A pattern of incisions like that shown in Figure 7 was made in the left cortex of case 6 two months after the control operation on the right side and one approximately like it on the left side in case 7 ten weeks after the operation on the right side. The incisions were extended into the depths of the central fissure both on the rostral and caudal sides and into the arcuate fissure on the caudal side. In case 7 the incisions went deep into both walls of the intraparietal fissure as well. The incisions anterior to the central fissure were made with blades 3.0 mm. in length. The results in the two animals were roughly similar.

The first day after operation the arm movements in running appeared to be almost normal except for slight favoring of the affected arm. The hand was regularly placed palm down as it is not after removal of area 4. The arm was used in climbing and the fingers hooked onto the cage wires, but the grip was noticeably weak and the hand occasionally slipped. During the first two days after operation the animals attempted a few times to reach for food with the affected hand but the fingers seemed unable to grasp even small objects which they touched and use of the hand in this manner was soon given up. Manipulative movements of the fingers began to reappear between the third and sixth days when the affected hand was used to help hold food at the mouth while eating. By the 10th day food was occasionally picked up by the affected hand alone. By the 15th day the affected hand and fingers were being used with moderate strength and agility with little evidence of motor impairment remaining except for a partial preference for use of the opposite hand by case 6.

It was found that the incisions on the left side had gone completely through the gray matter posterior to the central fissure and through approximately the upper half of layer VI in the precentral region. The cuts in the walls of the fissures extended well into the depths of the gray matter. At numerous points extra damage had been caused in the fissures by tearing of the pia and invasion of the medulla.

Control lesions in case 7. Three months after the first operation on the right side when all motor deficit in the left arm had long since disappeared the right hemisphere was again exposed. Brief electrical stimulation of the subdivided motor area evoked typical movements of the contralateral arm and hand. Almost the entire transected area was then destroyed. Biopsy specimens including the region of the central fissure were extirpated for sectioning and the remainder was removed by suction. The mass lesion was restricted more closely to the arm area particularly on the lateral border than were the incisions.

In the course of a month the affected hand had come to be used with some grip in climbing but it still was not used at all for manipulation. At this time a similar operation was performed on the left hemisphere. Motor impairment from the previous incisions on this side were no longer evident. This second lesion left the monkey quite helpless. It was now unable to use either hand for eating and had difficulty even in maintaining its balance when moving about. The legs on both sides were also partially affected. For two weeks the animal was given soft food which it took from a spoon the first six days and thereafter managed to eat directly from an elevated dish. If the dish were left on the floor so the monkey had to lean forward to reach it, the animal lost its balance and fell. In the course of the next three weeks the animal recovered sufficiently so that it could pick up its food with its mouth from the floor of the cage without falling over and could pull itself slowly up and down the wire walls of its cage.

Eight months later there had been but little improvement. It was still unable to use the hands for manipulating food which had to be picked up directly with the mouth. When bits of food escaped from between the lips during chewing, the hands were not able even to push it back into the mouth. The animal was still extremely slow and clumsy and appeared to tire quickly. The grip in climbing was weak and consisted merely of hooking the ends of the fingers over the cage wires. It was not possible to elicit any voluntary grip on sticks thrust against the hands. The arms occasionally crossed on each other beneath the body. This profound and lasting paralysis constituted an extreme contrast with the normal motor behavior which had been restored rapidly in this and other animals in which the corresponding cortical area had been subdivided by vertical incisions. The rapid recovery of normal motor function following subdivision of the whole sensorimotor arm area, the elicitation of typical motor reactions by stimulation of the partitioned cortex, and the subsequent permanent paralysis caused by removal of the same area in this animal provided

together impressive demonstration that the motor cortex was capable of carrying out its organized function in spite of such vertical incisions.

When the lesions were checked anatomically it was found that they had destroyed the cortical areas intended. In addition, the lesions in the central fissure had extended deep enough in the upper portion of the arm area apparently to interrupt some of the more superficial fibers to the trunk and leg cortex which accounted for the observed partial paralysis of the legs.

Case 8, right and left hemispheres. Vertical incisions as shown in the diagrams (Fig. 8) were made in the right and left hemispheres, the left side being done three weeks after the right. The depths of the blade which was used anterior to the central fissure was 3.1 mm. on the right side and 3.2 mm. on the left. On both sides the incisions went deep in both

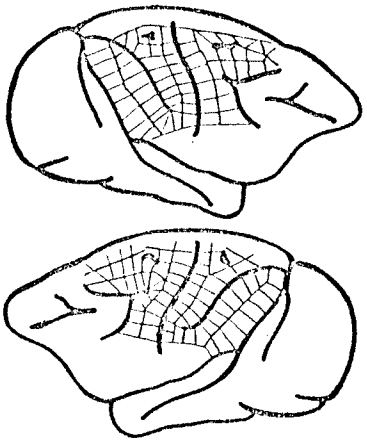


FIG. 8

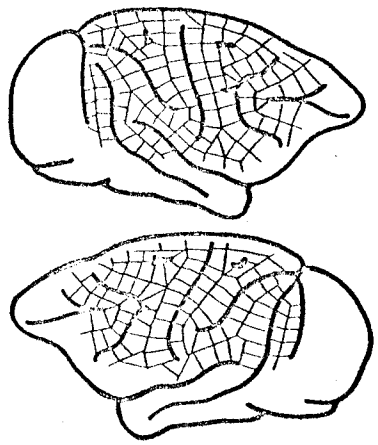


FIG. 9

walls of the central fissure and in the caudal wall of the arcuate fissure. The results on the two sides were roughly similar. There was practically complete elimination of manipulative movements of the fingers of the affected hand during the first five days after operation on the right cortex and during the first two days on the other side. In rapid running and climbing movements, however, very little motor deficit was noticeable; the affected arm was used independently with normal coordination at shoulder, elbow, and wrist but with some weakness evident in the grasp of the fingers. Manipulative movements were recovered rapidly until no further motor impairment was apparent by about the 15th day. Normal finger and hand coordination was restored in the manipulation of food, grooming, emptying of food pouch, tugging at collar, fending off sticks, etc. Between nine and twelve days after the second operation this animal was taught to overturn one of two cups for food, and to release pieces of food presented in a clamp at the end of a stick. There was no indication that the motor learning involved in these or other common performances was in any way subnormal.

It was found that the incisions posterior to the central fissure had extended well through the cortex. Anterior to the central fissure in the motor area where the cortex was thickest the cuts extended deep into the lower half of layer VI on the right side, while on the left side they went approximately to the inferior margin of this layer. The cuts reached well into the bottom of the central fissure and several entered the white matter farther than intended, particularly on the caudal side. Only a portion of the anterior wall in the depths of the arcuate fissure in the medial part of the arm region on the right side had escaped uninvaded.

Case 9, right and left hemispheres. The operations in this case were the same as those in case 8 except that the incisions were extended over a slightly wider area as indicated in the diagrams (Fig. 9) and went deep in both walls of the arcuate and intraparietal fissures as

well as in the central fissure. The cutting blades were the same depth as in case 8. The left side was done 15 days after the right. The immediate functional depression was not quite so severe as in the previous case. On each side the affected hand was used to assist the opposite hand in manipulating food on the day following the operation. On the fifth and sixth days the monkey started to use the affected arm for reaching and picking up small objects. By the 14th day after the first operation and by the 12th day after the second operation the hands were being used almost interchangeably without any signs of motor deficiency. Even the finest, most delicate voluntary movements appeared to have survived. Among other acts the monkey peeled bananas, picked up small bread crumbs individually, twisted orange peels inside out, wiped its eyes, emptied its food pouch, scraped a dish pan and licked the fingers individually with turning of the wrist and differential flexion and extension of the digits all in a normal manner. On the 16th day small pieces of apple were swung swiftly past the cage on a string attached to a pole. The animal exhibited excellent timing, directional accuracy and strength of movement in snatching these small rapidly moving objects out of the air as they swung past the cage.

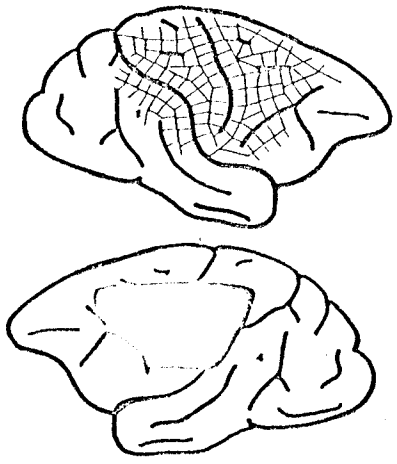


FIG. 10

Microscopic examinations of the sectioned brain showed that the incisions extended approximately through the depth of the cortex to the medulla in all except the frontal regions where the deeper cortical layers are extremely thin and drawn out. At a few points in the thickest part of the precentral area on the right side some of the cuts did not extend quite through layer VI although even at the minimum they went more than three-fourths of the way through this layer. Posterior to the central fissure on both sides the cuts reached completely through layer VI. In the central fissure the cuts went to the lower margin of the involuted gray matter but there was less damage to the medulla than in case 8, especially within the arm region. On the right side the incisions went into the depths of the arcuate fissure but on the left side they reached only about half-way down the walls of this fissure. The incisions extended to the bottom of the intraparietal fissure in the shallow portions in the arm region though not at its deep medial end.

Case 10, spider monkey, right and left hemispheres. A bilateral operation was performed in which the right cortex was sliced as shown in the diagrams (Fig. 10), and on the left side a smaller corresponding cortical area as indicated in the figure was removed en masse by suction. The depth of the knife blade used in the motor and premotor areas on the right side was 3.3 mm., that in the frontal area 3.0 mm. and that in the regions posterior to the central fissure, 2.7 mm. On the right side the incisions dipped into the fissure as indicated in Figure 1 and on the left side the depths of the fissures were left intact.

The result on the following day was a profound paralysis of the right arm with the right leg severely affected also. The limbs on the right side were not used at all, even in standing or climbing, and they were allowed to remain in awkward abnormal postures. The left arm and leg were extremely weak but were used to lift the animal and to hold it upright. The fingers of the left hand were used to grip the wires of the cage but were not used to pick up food. It was not until the tenth day after operation that the left hand was used for manipulation of food. Use of the left arm showed steady improvement thereafter, until at the end of two months motor deficit was no longer noticeable. On the right side, by contrast, recovery had progressed very little. The right arm was used weakly in climbing and no longer assumed extremely abnormal postures, but it still was not used in manipulative movements. Eigth months later, long after recovery on the left side, the right hand was still unable to grip a stick and was never used to pick up or hold food or even to help the left hand with unwieldy objects.

Histological examination showed that the cuts in this case reached well through the cortex including all of layer VI throughout the precentral motor area. In the frontal area

only the lower third of layer VI remained undivided, while in the postcentral area the cuts consistently extended through all cortical layers into the white matter.

Case 11, spider monkey, right and left hemispheres. The cortex on the right side was subdivided with incisions as shown in Figure 11. The incisions anterior to the central fissure were made with a blade 3.0 mm. in depth and throughout they dipped into the fissures as illustrated in Figure 1. On the following day the left arm and hand were used quite well in climbing. Several times the left hand was used in reaching for food, lifting it to the mouth and holding it while biting it into pieces. The right hand was usually preferred, however. Recovery was rapid until by the third day the hands were used almost interchangeably with little evidence of motor impairment.

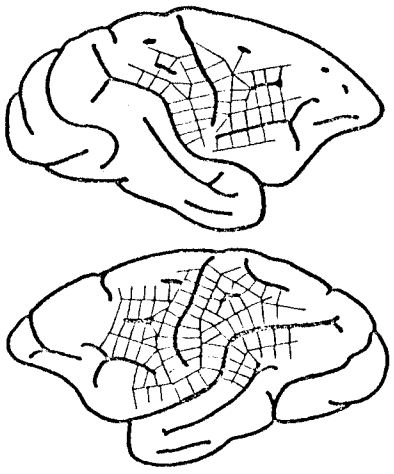


FIG. 11

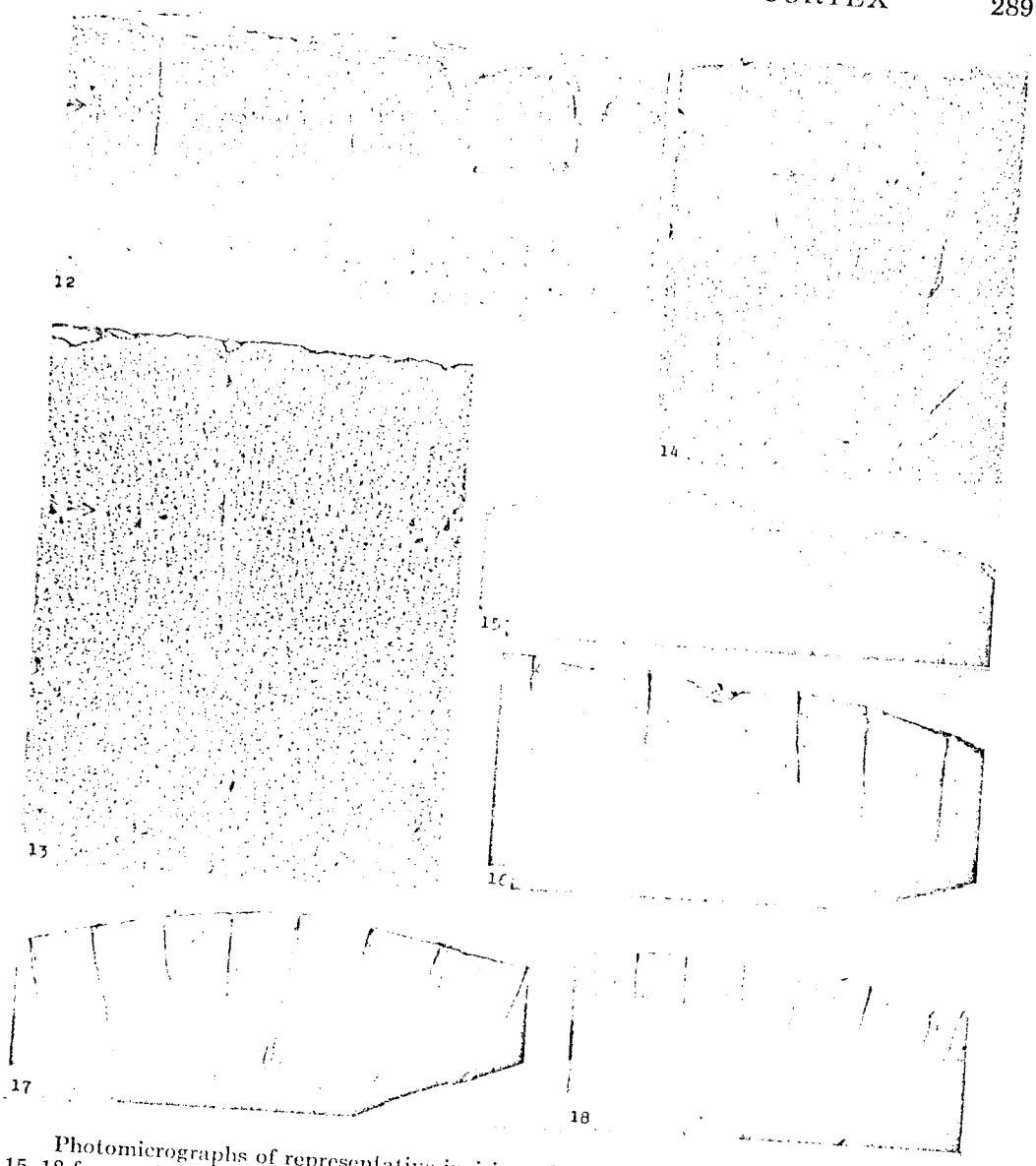
Ten days later a similar operation was performed on the left side. In this case the depression of function was a little more severe during the first two days. On the third day, instead of improving, it became markedly worse. A few days later it was found that an extensive infection had developed around the bone flap. This animal had been very thin and weak from the beginning of the experiment. It was approximately ten days before the use of the arm began to improve again. After twelve days more, motor deficit was no longer noted except that some preference for the contralateral arm still persisted.

As in all the previous cases the cuts posterior to the central fissure were found to extend completely through all cortical layers into the medulla. In area 6 the incisions went just to the deep margin of the cortex. In area 4 they extended through approximately seven-eighths of layer VI. The fresher cuts in this animal appeared to be slightly deeper than those in the opposite hemisphere although both were made with the same knife. This suggested that the incision scars may undergo some contraction during their formation which makes them appear shorter than the original cuts. This was indicated also by comparison of older cuts and fresh cuts in other cases.

The results in the spider monkeys were consistent in essential aspects with those in the macaques. In the spider monkeys, however, the functional depression from the cortical lesion as produced both by knife cuts and by mass destruction tended to be more severe.

DISCUSSION

It is evident from the results that well-organized function of the sensorimotor arm cortex was still possible after extensive subdivision of the arm fields of both hemispheres by vertical knife cuts. So long as the incisions divided only the gray mantle through the upper part of layer VI without entering the transition zone of overlap between medulla and cortex the motor disturbances were extremely slight and transient. When confined to the exposed surface of the cortex such incisions failed to disrupt even fine manipulative movements of hand and digits as early as a few hours after operation. When the walls and depths of the fissures were also involved, a partial impairment of movements ensued but recovery was practically complete in as early as ten days. The symptoms were found to increase rapidly in severity and duration when the cuts went deep enough to extend through the transition zone in the lower part of layer VI and into the white matter. The immediate effects of deep incisions invading the white matter approached



Photomicrographs of representative incisions. Figs. 12–14 stained for nerve cells and 15–18 for myelin. Figs. 12, 13, 14 and 16 are from precentral motor area. Arrows indicate layer of giant pyramidal cells. The incisions to the right in Fig. 12 and to the left in Fig. 14 appear wide because their plane is close to plane of section. Fig. 17 is from the anterior wall of central fissure. Figs. 15 and 18 are from postcentral gyrus. Length of knife blade used in Figs. 12, 13, 16, and 17 was 3.0 mm., that in Fig. 14 was 3.5 mm. and that in Figs. 15 and 18 was 2.7 mm. The Figures in order are from cases no. 7, 11, 6, and 8, with the last three from an animal the brain of which was operated upon in the same way as the left hemisphere of case 6. This animal expired without recovering from the anesthesia, whereupon the brain was fixed and sectioned to obtain a picture of the cuts in the fresh condition. Magnification varies in the different figures approximately from 3.5 times in Fig. 17 to 35.0 times in Fig. 13.

closely in severity those of ablation. Recovery, however, was much more rapid and thorough. Even in those animals in which deep incisions extended throughout the whole arm region, including the walls and depths of the fissures, impairment of function was no longer detectable by 24 days after operation.

Thus with the electrostimulable foci in the cortex for movement of shoulder, elbow, wrist, and digits as well as corresponding sensory foci separated from each other by radial incisions in both hemispheres as described, and with the whole arm cortex separated from its neighboring cortical fields, the coordination of the limb with respect to the trunk and of the various limb segments with respect to each other was nevertheless carried out in normal manner. Well-organized motor function survived even in the case of refined "voluntary" manipulative movements of hand and digits which presumably are most highly dependent on cortical control. Such symptoms as were observed were temporary and, it is important to note, were almost entirely symptoms of afunction, *i.e.*, muscular weakness, rather than of positive dysfunction such as convulsive, discoordinated, choreiform, spasmodic or athetoid movements. More than with simple mass destruction of tissue, lesions of the sort involved ought to have produced positive malfunction among the remaining active parts with consequent muscular incoordination, had any important organizing mechanism been disrupted.

The results suggest that horizontal intracortical interaction between various functional foci of a cortical field is by no means as extensive and fundamental a constituent of cerebral integration as has frequently been assumed. Neither those theories postulating important integrative effects from irradiation of definitive impulses or of waves of impulses through the fiberwork of the gray matter nor those theories postulating cerebral organization by horizontal spread of mass electrical potentials and field forces across the cortex find any verification in the results. Instead the evidence supports the view that interaction between separated loci across the cortex is achieved almost entirely by the systems of axons passing into the white matter, and that intracortical integration itself is largely vertical. This deduction is in full accord with the descriptions of intracortical synaptic relations reported by Lorente de Nó (24) in which it is pointed out that intracortical connections are established chiefly in the vertical direction with the cells of the various layers linked together in vertical chains.

The results can be considered decisive with regard to the interruption of horizontal intracortical transmission of discrete nerve impulses. Because of the lack of neuronal regeneration in the mammalian central nervous system (6) and from the microscopic appearance of the cortical scars it can be concluded definitely that the incisions formed permanent blockades to the horizontal conduction of excitations over definitive fiber pathways.

That the incisions also interrupted, or at least caused marked distortion of, all mass electric currents and field potentials capable of integrative effects cannot be stated so positively, although it seems probable. What evidence

there is indicates that self-propagating intracortical potentials cannot spread their excitatory effects across a fresh cut in the mammalian cortex (3, 8, 23, 27, 30). That propagation of such potentials across the cuts might be possible after the blood clots were removed is conceivable although it seems likely that the irregular sheet of scar tissue which replaced the blood clot might also form an effective barrier, or at least a very distorting influence. In any case the lack of discoordination in those animals in which the white matter was not invaded, even during the first few days after operation when the partitions of clotted blood must certainly have caused extreme distortion of any field forces playing in the area, suggests that cortical integration is not dependent upon such factors. Furthermore, according to proponents of field theory of central nervous organization, the patterns of field forces are supposed to be molded and remodeled by submicroscopic changes left in the cortex in the traces of previous experience (14, 15, 16). If such minor molecular alterations in the cortex are able to modify the mass potential patterns, how great a distorting influence should have been these macroscopic lesions.

That mass electrical potentials or field forces of the type under consideration normally have important integrative roles in cerebral function remains as yet entirely speculative. The current tendency to have recourse to hypotheses of this sort has arisen largely from the apparent inability to reconcile older concepts of stable neuronal linkages with the tremendous variety, plasticity, and diffuseness of cerebral functions on the one hand, and with the field character of many subjective perceptual phenomena on the other. The assumption of psycho-neural isomorphism involved in the latter instance seems to have no sound logical basis; while in regard to the former, the endowment of the central nervous system with properties for massive conduction is in direct opposition to the evident trend away from homogeneity and toward greater differentiation apparent in the evolution both of neural structure and function. An elaborate, highly differentiated and efficiently insulated connection system is much better qualified to manage complex plastic functions than is a homogeneous mass conductor.

The above interpretation implies that the temporary symptoms, where observed, were not due in any appreciable measure, if at all, to the disruption of horizontal intracortical transmission of integrative agents, but to other factors. The close correlation between the degree of functional disturbance and the extent to which the incisions invaded the white matter suggests that the symptoms were due mainly to the cutting of medullary fibers. Damage to cortical tissue produced directly by the knife and by shearing forces in the tissue adjacent to its path, along with the interruption of local neuron circuits through a zone of unknown width surrounding the incisions, must also inevitably have contributed their share to the depression of function. Other factors to be considered are hemorrhage, edema, swelling and pressure, and possibly adverse effects from the damaged tissue, and from the processes of clearing away tissue debris, healing and scarring. Presumably factors such as the above decreased the amount of intact cortex and also contributed to a

3. The functional symptoms which were observed were characteristic entirely of depression and afunction rather than of positive disorganization, and they appeared to be correlated primarily with invasion of the white matter.

4. The results fail to confirm theories of brain function which have assumed that horizontal intracortical transmission either of discrete excitations or of mass field forces plays any major or essential role in cerebral organization.

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